

**REMARKS/ARGUMENTS**

Status of Claims

Claims 1 and 10-14 are pending in the application. Claims 1, 12 and 13 have been amended. Claims 9 and 21-26 were subject to restriction and/or election requirement and have been withdrawn. Claims, 2-8, and 15-20 have been canceled.

Amendments to the Claims

By the above amendments, Claims 1, 12 and 13 have been amended. Claims 1 has been amended to clarify the claimed invention. More particularly, Claim 1 has been amended to clarify the recitation, in the alternative, of a stereochemically isomeric form or an N-oxide form thereof, and further address the unintentional errors in antecedent basis. Claims 12 and 13 have been amended to correct unintentional typographical errors and to remove the recitation of the term "derivatives thereof". Applicants' attorney submits that the amendments are fully supported by the disclosure in the specification, as originally filed. These amendments are submitted to clarify what applicant regards as his invention and does not introduce new matter into the claim. Applicants reserve the right to present the subject matter removed from these claims in a continuation application. Accordingly consideration and entry of this amendment is requested.

Claim Objections

Claims 12-13 have been objected to for typographical errors. Applicants' attorney respectfully refers the Examiner to the above amendments of Claims 12-13 which correct the unintentional typographical errors and which further remove recitation of the term "derivatives thereof". In view of the amendments, Applicants' attorney respectfully request the objections be withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 12-13 have been rejection under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. More particularly, the Examiner alleges that the written description requirement has not been met for the term "derivatives thereof".

Without conceding the correctness of the rejection, and solely for the purpose of advancing the prosecution of the instant application, Claims 12-13 have been amended to remove recitation of the term "and derivatives", thereby rendering the rejection moot. Applicants' attorney respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1 and 10-14 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard a the invention. More particularly, the Examiner states that in Claim 1, 1) it is unclear what "thereof" is referring to; 2) it is unclear if the pharmaceutical composition comprises a stereochemically isomeric form and an N-oxide form in addition to the other components; and 3) that the terms "the stereochemically isomeric forms" and "the N-oxide form" lack antecedent basis.

Applicants' attorney respectfully refers the Examiner to the above amendments of Claim 1, which amendments rewrite the claim to clarify the claimed invention. More particularly, Claim 1 has been amended to recite:

A pharmaceutical composition comprising  
a pharmaceutically acceptable carrier and,  
as active ingredients,  
    (a) an opioid analgesic and  
    (b) (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof;

wherein the (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, pharmaceutically acceptable acid or base addition salt thereof, stereochemically isomeric form thereof or *N*-oxide form thereof is present in an amount effective to reduce the respiratory depression caused by the administration of the opioid analgesic.

Applicants' attorney respectfully submits that in view of the above amendment, the claim meets the requirements of 35 U.S.C. §112, second paragraph, in that it particularly points out and distinctly claims the invention. More particularly, the claim as amended clarifies that the pharmaceutical composition comprising three components: a first component of a pharmaceutically acceptable carrier, a second component of an opioid analgesic and a third component of (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof. Applicants' attorney therefore respectfully request that the rejection of Claims 1 and 10-14 under 35 U.S.C. §112, second paragraph b withdrawn.

#### Rejection under 35 U.S.C §103(a)

Claims 1 and 10-14 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over US Patent 5,880,132 in view of US Patent 6,197,772.

Applicants' attorney respectfully traverses the rejection. Applicants' attorney respectfully submits that the disclosure in US 5,880,132 teaches a combination of a tachykinin antagonist and an opioid analgesic at a sub-maximal dose to reduce the likelihood of side-effects associated with opioid analgesic use (including respiratory depression). US 5,880,132 does not, however, teach or suggest the use of (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base

addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof in combination with an opiod analgesic. US 6,197,772 teaches (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide for the treatment of pain, emesis or asthma, but does not teach or suggest the compound in combination with opiod analgesics.

Additionally, Applicants' attorney submits that the disclosure in US 5,880,132 teaches limiting or decreasing the dosage amount of the opiod analgesic as a means for avoiding respiratory depression, as well as for the purpose of limiting the development of tolerance and dependency; and further a means for compensating for the decreased pain relief due to the lower opiod dosage by adding a tachykinin antagonist. US 5,880,132 does not teach or suggest the use (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof or any tachykinin antagonist for reducing the respiratory depression caused by the administration of the opiod analgesic.

By contrast, the present invention is directed to a combination of an opiod analgesic and (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof; wherein the opiod dosage is not necessarily sub-maximal or otherwise limited; and wherein the (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof is provided at a dosage level which reduces the respiratory depression caused by administration of the opiod analgesic.

Applicants' attorney further respectfully submits that contrary to the Examiners' statement, it would not have been obvious to one skilled in the art that to use (+)-(B)-*trans*-

4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-N-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof in combination with an opioid analgesic to decrease respiratory depression. In fact, one skilled in the art would not turn to the teachings in US 5,880,132 for teachings of methods of overcoming or counteracting adverse effects of opioids, including respiratory depression, since the disclosure in US 5,880,132 does not teach or suggest any means or compounds for overcoming or counteracting the respiratory depression associated with opioid analgesics, but rather teaches decreasing opioid dosages as a means of avoiding respiratory depression and other adverse effects and compensating for the decreased efficacy with a tachykinin antagonist.

Thus Applicants' attorney respectfully submit that the teachings in US 5,880,132 and US 6,197,772, either or alone or in combination would not motivate one skilled in the art to combine (a) an opioid analgesic and (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-N-(2,6-dimethylphenyl)-1-piperazine acetamide, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or an *N*-oxide form thereof; wherein the (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidiny]-N-(2,6-dimethylphenyl)-1-piperazine acetamide, pharmaceutically acceptable acid or base addition salt thereof, stereochemically isomeric form thereof or *N*-oxide form thereof is present in an amount effective to reduce the respiratory depression caused by the administration of the opioid analgesic.

Applicants attorney therefore respectfully requests that the rejection of Claims 1 and 10-14 under 35 U.S.C. §103(a) under 35 U.S.C. 103(a) as allegedly unpatentable over US Patent 5,880,132 in view of US Patent 6,197,772 be withdrawn.

### **CONCLUSION**

The Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/PRD2077USPCT1/HBW.

Early favorable action on the merits is respectfully requested. Applicant respectfully requests that a timely Notice of Allowance of Claims 1 and 10-14.

Respectfully submitted,

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